Integration with Anatomy in Curriculum

It marvels me that men like Vesalius and Caius and physicians right up to the turn of this century so greatly stressed anatomy's importance. In their clinical practice it could have had little application. They could not do much more than look at the tongue and urine, palpate the abdomen and examine the chest, and in recent times listen to the heart. This could hardly be called applied anatomy.

Now every doctor can see many aspects of anatomy depicted by radiology, and the spectrum widens almost daily. Surely, anatomy is very much more important today than ever it was, but a complete reorientation is necessary in its teaching and application. The 2nd M.B. medical student starts with great enthusiasm and dedication. When he has finished his "dry as dust" anatomy dissecting a smelly, senile, desiccated, cachectic corpse he has lost most of his enthusiasm. Anatomy must be made to live and only those teachers who see patients can make it live.

The other day I was privileged to sit unknown at the back of the anatomy lecture theatre at King's College, Strand, listening to Dr. Oscar Craig (Consultant Radiologist at St. Mary's Hospital), lecturing on radiological anatomy to 2nd M.B. students. It was the most refreshing experience I have had for a long time. The theatre was packed and one could have heard a pin drop, they were so attentive. They were being exposed to live medicine. We asked them to let us have their comments in writing. I will quote a typical example. The student wrote:

"1. Radiology is the only means of bringing living anatomy into a course so remote from surgery and casualty.

2. It reminds one that surgery is not the only thing one needs to know anatomy for.

3. It makes the course interesting—vital."

In this connexion you may have read a recent article in the *Lancet*.[25] Dr. M. A. Simpson, a psychiatrist at McMaster University, Hamilton, Ontario, writing on "A Mythology of Medical Education" had this to say:

"Students can cope surprisingly well with clinical problems from their earliest weeks at medical school; not playing at being sham doctors but learning the language and principles of the basic sciences via clinical problems. In this way they can appreciate the beauty and the excitement of sciences that all too often present themselves as appallingly dull. These sciences are too important to be treated in this way."

"Students learn more effectively material which they perceive as relevant to the future practice of medicine. But it is they who must recognize the relevance; it is not enough that the teacher or dean perceives it as relevant."

We know that the teaching of anatomy is in the melting pot, so let us get its future right. I would like to see an authoritative committee set up to make recommendations concerning its teaching in its relation to radiology. Remember it was a President of this College who introduced and established the science of anatomy in this country over 400 years ago. I must interpolate here that what I have in mind is not a surgical problem, but rather anatomy for general practitioners and physicians and all non-surgical medical men. The would-be surgeon would obviously receive additional training in classical anatomy as a postgraduate.

I would appeal to you, Mr. President and Censors, to establish a committee of appropriate experts to look into and report on this important problem.

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Clinical Problems

Complications of Carbenoxolone Therapy

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Summary

Side effects from carbenoxolone are common and are due to electrolyte disturbance, such as sodium retention and hypokalaemia. They occur particularly in the elderly, who may already be being treated for other illnesses. Eight patients are described with serious side effects from carbenoxolone therapy, some of which were unrecognized for some time because of inadequate follow-up or because clinicians were unfamiliar with them.

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Introduction

Carbenoxolone, a triterpenoid compound, accelerates healing of gastric ulcers,[1 2] and is widely used. While the side effects

are known, they have received little prominence in reports and we would like to draw attention to them. Side effects are common and related to electrolyte disturbance. Hypokalaemia may occur with a myopathy,[3-5] or nephropathy,[6] while sodium retention may precipitate headaches, hypertension, or cardiac failure.[7] Eight patients are described with serious side effects illustrating the various clinical problems of carbenoxolone toxicity.

Case Histories

Case 1

Case 1 presented with features of an intracranial tumour.

A 54-year-old woman was admitted with a haematemesis and found to have a small gastric ulcer on barium meal examination. The blood pressure was 120/70 and the serum potassium 4·3 mM/l. She had had migraine in the past but had been free from attacks for 10 years. Carbenoxolone, 150 mg daily, was given but the patient discontinued treatment after 14 days because of ankle oedema. She was readmitted after five weeks with abdominal pain; the blood pressure was 150/90. Carbenoxolone, 150 mg daily, was given for a further eight weeks and during this time the patient was not seen in the outpatient department. She developed a right-sided headache and vomited repeatedly for about three weeks. Her family doctor, who recorded a blood pressure of 210/130, stopped the carbenoxolone and gave clonidine, 0·3 mg daily. After a further two days she was admitted to hospital, drowsy and complaining of severe headaches. There was a left homonymous hemianopia with left-sided sensory inattention and both plantar responses were extensor. The blood pressure was 150/90 and the serum potassium 2·6 mM/l.

A tentative diagnosis of a cerebral tumour involving the right hemisphere was made. The electroencephalogram showed a delta wave focus in the right temporal area but the results of the skull *x*-ray film, isotope cerebral scan, cerebrospinal fluid examination, and right carotid angiogram were all normal. Five days after admission her headache began to improve but she then experienced bizarre organized visual hallucinations. These distressing hallucinations subsided after 48 hours and the E.E.G. also became normal.

When she was seen later in the outpatient clinic there were no neurological signs. It was thought that carbenoxolone had precipitated hemiplegic migraine involving the pre-occipital cortex.

Case 2

Case 2 developed impairment of vision and papilloedema.

A 64-year-old man was found to have a duodenal ulcer and given carbenoxolone, 300 mg daily for one week and 150 mg daily thereafter. The blood pressure initially was 140/100. He was discharged after one week but complained of mild headaches and the blood pressure had risen to 200/110. He was seen two months later, still complaining of mild headaches, and the blood pressure was again 200/110. After 13 weeks' treatment with carbenoxolone his family doctor referred him to the ophthalmology department because of blurred vision and loss of vision in the right eye. The headaches had been severe for three weeks. The blood pressure was now 220/140 and he had a hypertensive retinopathy with papilloedema and numerous haemorrhages. The serum potassium was 2·1 mM/l. Carbenoxolone was stopped and the blood pressure controlled by small doses of clonidine and spironolactone. The serum potassium returned to normal after 10 days' treatment with supplements.

In this patient, carbenoxolone precipitated malignant hypertension with retinal damage.

Case 3

Case 3 developed left ventricular failure.

A 67-year-old man was admitted to hospital because of increasing weakness for one month; he had been taking phenylbutazone for gout. The blood pressure was 150/90, blood urea 12 mM/l., and the haemoglobin 8·3 g/100 ml, owing to iron deficiency. A prepyloric ulcer was seen on gastroscopic examination and he was sent home on carbenoxolone, 300 mg daily; Ferrogradumet, two daily, allopurinol, 300 mg daily; and indomethacin, 75 mg daily. He failed to keep his outpatient appointment and was readmitted as an emergency eight weeks later, still taking the carbenoxolone, and complaining of severe breathlessness and recurrent nocturnal dyspnoea. The blood pressure was 180/80. He had both ankle and sacral oedema with crepitations at the base of both lungs. The chest *x*-ray film showed pulmonary oedema. The haemoglobin was 9·2 g/100 ml, blood urea 12·5 mM/l., and serum potassium 2·6 mM/l. Carbenoxolone was stopped and the left ventricular failure resolved with diuretics; the hypokalaemia was corrected by oral supplements of potassium.

The inadvertently prolonged treatment with carbenoxolone, owing to failure to attend the outpatient department, was thought to have precipitated the cardiac failure.

Case 4

Case 4 presented with muscle weakness and cardiac failure.

A 79-year-old woman was admitted with a haematemesis due to a gastric ulcer. She was in mild congestive cardiac failure and had mitral valve disease and a blood pressure of 170/110. The serum potassium was 3·6 mM/l. and serum urea 4·0 mM/l. She was given frusemide, 40 mg, with potassium supplements (16 mEq/day) and digoxin, 0·0625 mg daily. In addition, she had 200 mg carbenoxolone for 13 days followed by 100 mg daily. An outpatient appointment was arranged for six weeks later but she failed to attend and was readmitted as an emergency after three months. At this time she complained of anorexia and appreciable generalized muscle weakness. She had gross peripheral oedema due to congestive cardiac failure. The blood pressure was 140/70, the serum potassium 1·8 mM/l., the urea 6·4 mM/l., and the creatine phosphokinase 1,130 mM/ml (normal <110 mM/ml). Carbenoxolone was stopped and the hypokalaemia corrected by potassium supplements.

Carbenoxolone was considered responsible for the increase in cardiac failure while thiazide diuretics had contributed to her hypokalaemia. Prolonged treatment with carbenoxolone was again due to failure to attend the outpatient clinic.

Case 5

In case 5 diagnoses of the Guillain-Barré syndrome and primary hyperaldosteronism were made.

A 54-year-old man came to a neurology department with a three-day history of limb weakness and numbness in his hands and feet. The weakness was most definite in his legs and he had minimal sensory loss with a glove and stocking distribution. A diagnosis of the Guillain-Barré syndrome was made and he was admitted to hospital. He had ankle oedema and the blood pressure was 220/160. The serum potassium was 1·6 mM/l., bicarbonate 40 mM/l., and urea 4·5 mM/l. The cerebrospinal fluid was normal. The hypertension was treated with alpha-methyl-dopa, frusemide, and potassium supplements (96 mEq daily), but after two weeks the serum potassium and bicarbonate levels were unchanged and a tentative diagnosis of primary hyperaldosteronism was made.

A single measurement of blood pressure three years previously had been 180/120, but no treatment was given. When he was first seen in the neurology department it was noted that he had received treatment for epigastric pain due to a duodenal ulcer in the previous weeks, but little attention was paid to this. He had been taking carbenoxolone, 200 mg daily for six weeks.

He was referred to another hospital for further investigations, where his blood pressure was found to be 210/130 and the serum potassium 2·3 mM/l. Urinary aldosterone secretion over 24 hours was 0·2 pg (normal range 5-20 pg). The carbenoxolone was stopped and potassium supplements over the next month corrected his symptoms and hypokalaemia.

The profound hypokalaemia, caused by carbenoxolone, was difficult to reverse and the relation between carbenoxolone therapy and the patient's symptoms was not recognized for several weeks.

Case 6

In case 6 hypokalaemia was complicated by a cardiac arrest.

A 73-year-old woman was admitted to hospital with a gastrointestinal haemorrhage from a large gastric ulcer. She was given

carbenoxolone, 300 mg daily for one week and 150 mg daily thereafter. When treatment was started the blood pressure was 130/80, the serum potassium 4·2 mM/l., and urea 7·6 mM/l. She was too ill to keep an outpatient appointment three weeks later and instead was readmitted after six and a half weeks as an emergency with profound muscle weakness. She said that two days after leaving hospital she had developed ankle oedema and such severe weakness that she was unable to stand. In addition, she had had several attacks of paraesthesiae involving the left side of her face, the left arm, and leg. On examination there was gross weakness of all limbs, particularly involving the proximal muscles. The pulse was coupling and an electrocardiogram showed sagging of the S-T segments, flat T waves, and prominent U waves with frequent extrasystoles. The serum potassium was 1·6 mM/l., bicarbonate 40 mM/l., and urea 4·0 mM/l.

Twenty-four hours after admission she collapsed, became cyanosed, and pulseless. She was resusciated by external cardiac massage and gradually regained consciousness. Supplements of potassium were given (214 mEq daily) and after 19 days the serum level was 3·6 mM/l. and her muscle weakness had recovered.

Severe muscle weakness developed in the first week of therapy and she had symptoms consistent with transient cerebral ischaemia. The hypokalaemia probably caused the cardiac arrest.

Case 7

Case 7 presented initially with unilateral weakness.

A 52-year-old man who had three previous myocardial infarctions was found to have a lesser curve gastric ulcer on radiological investigation. He was given carbenoxolone, 150 mg; potassium supplements, 24 mEq; and hydrochlorothiazide, 100 mg daily. When he was seen in the outpatient department two weeks later he complained of breathlessness, ankle oedema, and weakness of the right hand. The carbenoxolone was stopped and the potassium supplements increased to 48 mEq daily. The serum potassium level at this time was 2·1 mM/l. During the next week he developed considerable weakness in his right arm and leg and was thought to have had a cerebrovascular accident. During the next few days the weakness also involved his left side and he was unable to walk unaided when he came to the clinic one week later. He had profound generalized muscle weakness and the serum potassium level was 1·8 mM/l. Intravenous supplements of potassium were given and muscle power improved rapidly.

Case 8

Case 8 developed generalized weakness.

A 58-year-old man was admitted to hospital with abdominal pain due to a large lesser curve gastric ulcer. He had mild hypertension (170/105) and was taking alpha-methyl-dopa, 500 mg thrice daily, and chlorthalidone, 50 mg daily. The serum potassium level was 4·4 mM/l. and urea 6 mM/l. Carbenoxolone, 300 mg daily, was given for the gastric ulcer.

When he was seen four weeks later he had great difficulty in walking because of weakness. The serum potassium was 1·6 mM/l., the bicarbonate 36 mM/l., and the urea 5·0 mM/l. The electrocardiogram showed sagging of the S-T segments with prominent U waves consistent with hypokalaemia. The chlorthalidone and carbenoxolone were stopped and potassium supplements (96 mEq daily) were given. The serum potassium returned to normal and the muscle weakness disappeared.

Discussion

Side effects from carbenoxolone due to sodium retention are frequent. Doll, Langman, and Shawdon[8] reported fluid retention in 60% of patients given 300 mg daily and in 45% receiving 150 mg; rises in diastolic blood pressure of over 20 mm Hg occurred in five of 10 patients given 300 mg daily and in two of 10 given 150 mg daily.[9] Hypokalaemia is less common, but values of less than 3 mM/l. occurred in five of 17 patients receiving 300 mg daily for duodenal ulcer.[10] The varied clinical presentations are not well recognized but are of importance. Headache, oedema, breathlessness, cardiac failure, angina, hypertension[11] and epilepsy[2] have all been reported in association with sodium retention. Hypokalaemia most commonly presents with muscle weakness and in previous reports, as in case 5, diagnoses of hyperaldosteronism have been considered.[12-14] Some patients have complained of peripheral paraesthesiae, as in our patient who was thought to have the Guillain-Barré syndrome.

In several of our cases there was some delay in recognizing the cause of the patients' symptoms, partly because clinicians in both hospital and general practice were not familiar with the side effects. There was also some reluctance to attribute such severe clinical problems to the effect of medical ulcer therapy, which traditionally has been safe.

Side effects occur particularly in the elderly and in patients with renal, cardiovascular, and hepatic disease. Four of our patients were aged over 60 and three were receiving a diuretic for cardiac failure. Nevertheless, younger patients with no apparent contraindication to treatment may develop severe complications. The effect of hypokalaemia in patients with ischaemic heart disease receiving digoxin is potentially very serious. Two of our cases (6 and 8) showed gross changes of hypokalaemia on the electrocardiogram and one had a cardiac arrest.

Though carbenoxolone will accelerate healing in gastric ulcer the evidence that it is beneficial in duodenal ulcer is less convincing.[10 15 16] Two of our patients had a duodenal ulcer and one a prepyloric lesion. We have recently encountered patients who have been given the drug for upper abdominal pain without previous investigations. One proved to have pancreatitis and another recurrent small bowel intussusception. A clear demonstration of a benign gastric ulcer is probably the only indication for using the drug.

Follow-up of patients at the hospital was inadequate. Several patients failed to keep their appointments (cases 1, 4, and 6), in some instances because they were too ill to do so. While carbenoxolone is effective in the treatment of gastric ulcer there must be reservations about its safety. It should be prescribed with caution and careful supervision is essential.

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